of direction provided, (g) existence of working examples, and (g) quantity of experimentation necessary.

In the present case, the breadth of claims is narrow and the nature of the invention is simple, being drawn essentially to peptides comprising SEQ ID NO:23 (human PGP-2ac). The state of the prior art is relatively mature and complete regarding making recombinant polypeptides and performing receptor assays (these are routinely practiced techniques in most modern molecular cell biological laboratories) and the level of skill in the art is high, being at the Masters or Ph.D. level. The amount of direction provided in the specification is high, such that GFRα-RET activation assays are completely described and exemplified in the instant specification and the claimed polypeptides are completely described according to the written description guidelines (*i.e.,* as definite amino acid sequence identifiers). Evidence supporting the scientific theory that the GDNF F2a and F2c regions are necessary for GFRα1-RET activation and working examples of a persephin growth factor substituted with a GDNF "F2a" sequence (AFDDD) and a GDNF "F2c" sequence (YHILRKH) having GFRα1-RET specificity are provided in the specification (see Example 2 of specification at pages 32 and 33).

Finally, given the "considerable direction and guidance" in the specification (*i.e.,* the RET activation assays are spelled out in sufficient detail to allow the experiment to be repeated with a polypeptide of SEQ ID NO:23 or 26), the "high level of skill in the art" and a working example of a persephin substituted with GDNF "F2a" sequence (AFDDD) and a GDNF "F2c" sequence (YHILRKH), the quantity of experimentation that may be required to demonstrate specific GFRα1-RET activation activity of SEQ ID NO:23 or 26 is very low and thus not undue or unreasonable. The level of experimentation is reasonable, "since [at least] one embodiment and the method to determine [activity] was set forth in the specification, the specification [is] enabling." See *United States v. Telectronics, Inc.,* 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. Denied,* 490 U.S. 1046 (1989). Also, the level of experimentation is reasonable since the method of testing the two well described polypeptides of SEQ ID NO:23 and 26 is well described and demonstrated in a working example in the specification. It is a simple matter for the skilled artisan to test poly peptides of SEQ ID NO:23 or 26 as operable GFRα1-RET

agonists. Importantly, no modifications to the polypeptide sequences or to the method of testing GFRα1-RET activation are required, hence the level of experimentation is not unreasonable (see MPEP Section 2164.06(a)).

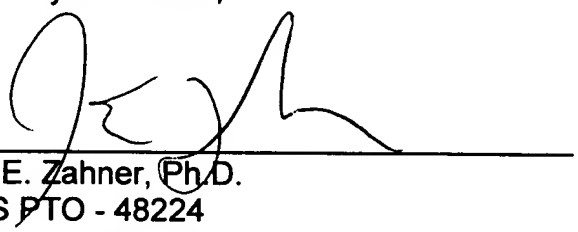
The crux of the Examiner's rejection is that one skilled in the art would not believe that a polypeptide comprising a human persephin that is substituted with the GDNF "F2a" sequence –AFDDD- and the GDNF "F2c" sequence –YHILRKH- would have specific GFRα1-RET activation activity, in view of a working example of a murine persephin that is substituted with the GDNF "F2a" sequence –AFDDD- and the GDNF "F2c" sequence –YHILRKH- having specific GFRα1-RET activation activity. Applicants assert that one skilled in the art, who in this case would be a Ph.D. or Masters level molecular cell biologist, would reasonably expect such a substituted human persephin (e.g., a polypeptide of SEQ ID NO:23 or 26) to have specific GFRα1-RET activation activity for the following reasons: (a) "Wild-type" human and mouse persephin are known in the art to have the same receptor specificity (activation of GFRα4-RET and not GFRα1-RET; see reference AW). (b) Example 2 of the instant specification establishes the scientific basis for the necessity of the GDNF "F2a" sequence –AFDDD- and the GDNF "F2c" sequence –YHILRKH- for activation of GFRα1-RET. (c) A human PGP-2ac and a mouse PGP-2ac are 85% identical and 94% similar to one another (see Exhibit C).

Furthermore, the Examiner's rejection of the claims, which essentially revolves around the alleged lack of a working example of human PGP-2ac having GFRα1-RET specificity, is improper since "lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement." (See MPEP Section 2164.02.)

In view of the amendments and arguments presented, Applicants believe that the claims are enabled by the specification-as-filed and therefore patentable. Applicants

respectfully request that the rejection of the claims under 35 U.S.C. § 112, first paragraph be withdrawn and the claims allowed to issue. If ther are any outstanding issues that need to be resolved, the Examiner is invited to call the undersigned agent.

Respectfully submitted,



Joseph E. Zahner, Ph.D.
Reg. US PTO - 48224
Thompson Coburn LLP
One US Bank Plaza
St. Louis, Missouri 63101
Telephone: 314-552-6354
Fax: 314-552-7354

MARKED-UP COPY OF AMENDED CLAIMS

1. (Twice amended) A polypeptide which activates GFRα1-RET but does not substantially activate GFRα2-RET or GFRα3-RET, wherein

(a) said polypeptide comprises a persephin as set forth in SEQ ID NO:1, [SEQ ID NO:2 or SEQ ID NO:3,] and further comprises substitutions in region F2a and substitutions in region F2c,

(b) the substitutions in region F2a comprise from one to eight amino acids that are [either] identical to region F2a of a GDNF family ligand, [or contain conservative amino acid substitutions of region F2a of a GDNF family ligand,]

(c) the substitutions in region F2c comprise from one to eight amino acids that are [either] identical to region F2c of a GDNF family ligand, [or contain conservative amino acid substitutions of region F2a of a GDNF family ligand,]

(d) the GDNF family ligand is a peptide [selected from the list consisting] of SEQ ID NO:4[, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9 and SEQ ID NO:10].

7. (Amended) The polypeptide of claim 1 [6], comprising SEQ ID NO:23[, SEQ ID NO:24 or SEQ ID NO:25].

8. (Amended) The polypeptide of claim 1 [6], consisting of SEQ ID NO:26[, SEQ ID NO:27 or SEQ ID NO:28].

EXHIBIT C

CLUSTAL W MULTIPLE SEQUENCE ALIGNMENT OF RODENT PGP-F2ac & HUMAN PGP-F2ac

```
SEQ ID NO:12 CRLWSLTLPVAELGLGYASEEKVIFRYCAGSCPQEARTQHSLVLARLRGRGRAHGRPCCQ
SEQ ID NO:23 CQLWSLTLSVAELGLGYASEEKVIFRYCAGSCPRGARTQHGLALARLQGQGRAHGGPCCR
             *.****** ************************. ***** * ****.*.***** ***.

SEQ ID NO:12 PTAFDDLVTFLDDQHHYHILRKHSAAACGC
SEQ ID NO:23 PTAFDDLVAFLDDRHRYHILRKHSAAACGC
             ********.****.*.***************
```

85/90 similarity

CLUSTAL W(1.4) MULTIPLE SEQUENCE ALIGNMENTS

```
SEQUENCE FORMAT IS PEARSON
SEQUENCE 1: SEQ ID NO:12 = RODENT PGP-F2ac                    90 AA
SEQUENCE 2: SEQ ID NO:23 = HUMAN PGP-F2ac                     90 AA

START OF PAIRWISE ALIGNMENTS
ALIGNING...
SEQUENCES (1:2) ALIGNED. SCORE:  85

START OF MULTIPLE ALIGNMENT
THERE ARE 1 GROUPS
ALIGNING...
GROUP 1: SEQUENCES:   2      SCORE:1190


CONSENSUS LENGTH = 90

CLUSTAL-ALIGNMENT FILE CREATED  [INTERNET.ALN]
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